SCIENTIFIC ABSTRACT OF THE PROTOCOL

The proposed study is designed to test the safety and biological efficacy of a cationic lipid:DNA complex (#67:DOPE:pCF1-CFTR) encoding the cDNA for the cystic fibrosis transmembrane conductance regulator (CFTR) when applied to the nasal epithelium of cystic fibrosis (CF) patients. The delivery vehicle consists of a novel cationic lipid (#67) combined with a neutral co-lipid (DOPE). Both the cationic lipid and the lipid:DNA formulation have been optimized for the transfection of CF epithelial cells *in vitro* and lung epithelial cells *in vivo.* The #67:DOPE:pCF1-CFTR complex is formed by mixing the delivery vehicle (#67:DOPE) with DNA (pCF1-CFTR) at the appropriate ratio and concentration. The pCF1-CFTR component has been developed to maximize expression of the CFTR cDNA in CF epithelial cells. Since preclinical toxicology studies suggest that toxicity is primarily due to the lipid portion of the complex, we have elected to test the lipid component alone in a dose escalation study in the nose of normal volunteers prior to testing the #67:DOPE:pCF1-CFTR complex in CF patients.

The protocol has two parts. Part A is a single dose, dose escalation study in which #67:DOPE is applied to the nasal epithelium of normal volunteers. A total of six volunteers will be recruited with two in each of three dosing cohorts. The first cohort will receive 0.8mg of #67:DOPE, the second cohort 4.0mg of #67:DOPE, and third cohort 8.0mg of #67:DOPE. The highest tolerated dose, as determined by the absence of: i) systemic toxicity, ii) significant local inflammation, and, iii) a change in the voltage across the nasal epithelium (Vt) that would preclude a reliable assessment of the measurement in CF patients, will be tested in CF patients.

Part B of the protocol will test the highest tolerated dose of #67:DOPE, as determined in part A, complexed to the corresponding dose of pCF1-CFTR (e.g. the 8.0 mg dose of #67:DOPE would be complexed with 5mg of pCF1-CFTR to give a 1:4 molar ratio). A total of six CF patients, in a single dosing cohort, will receive the #67:DOPE:pCF1-CFTR complex in one nostril and the same dose of #67:DOPE alone in the opposite nostril. These will be delivered using a catheter positioned along the inferior surface of the inferior turbinate. Administration will be double blind. Safety of the #67:DOPE:pCF1-CFTR complex will be assessed by nasal exams, measurements of inflammatory mediators in the nose and blood, by routine blood and urine analyses and assessment of pulmonary function. Efficacy will be assessed by comparing Vt measurements taken prior to treatment and for several days post-treatment. Additional evidence of gene transfer will be generated by RT-PCR analysis of cells obtained post-treatment by nasal brushing.

The successful outcome of this protocol will add to our knowledge of the safety and efficacy of lipid:DNA complexes and will guide the design of subsequent protocols targeted to the respiratory airways of CF patients.